



---

*Normal Human Blood Serum as a  
Curative Agent in Hemophilia  
Neonatorum.*

*A Preliminary Report, with Suggestions for its Use  
in Other Conditions.*

BY

JOHN EDGAR WELCH, M.D.,

PATHOLOGIST TO THE NEW YORK LYING-IN HOSPITAL, NEW YORK.

---

FROM THE  
AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1910



## NORMAL HUMAN BLOOD SERUM AS A CURATIVE AGENT IN HEMOPHILIA NEONATORUM.<sup>1</sup>

A PRELIMINARY REPORT, WITH SUGGESTIONS FOR ITS USE IN  
OTHER CONDITIONS.

BY JOHN EDGAR WELCH, M.D.,

PATHOLOGIST TO THE NEW YORK LYING-IN HOSPITAL, NEW YORK.

(From the Laboratory of the New York Lying-in Hospital.)



IN a study of a series of cases in which animal serum was administered to human beings it has been noted that certain symptoms appear regularly and in sequence. The first of these and the most frequent is fever, which is usually high and may vary from one to three degrees Centigrade. The fever is irregular and fluctuates in accordance with the amount of serum used, and remains until all other symptoms disappear. Shortly after the beginning of the fever certain rashes appear on the skin, the most troublesome of which is urticaria, which may begin at the site of injection and spread over the trunk and limbs. There may be considerable œdema in the neighborhood of the wheals, and often the itching is very intense and agonizing. Erythema usually follows the urticarial rash within two or three weeks. Scarlatiniform rashes also occasionally appear. Sometimes a morbiliform rash appears, and when it affects the face, accompanied by swelling and lachrymation, with congestion of the conjunctiva, is very suggestive of measles. The lymph nodes on the side of the body to which the serum has been administered first become enlarged and later others over the body. The enlargement is accompanied by tenderness. In some instances the joints become very painful and slightly reddened, and occasionally slight swelling occurs. General œdema of the body may occur and the weight increase, though there is diminished ingestion of food. The œdema may be accompanied by albuminuria and casts and blood in the urine. Some rare manifestations reported are: Hemorrhage into the bowel, urethral hemorrhage, œdema of the glottis, and diffuse bronchitis.

We not infrequently hear of sudden death following soon after

<sup>1</sup> Read at a meeting of the New York Academy of Medicine, March 31, 1910.

the administration of a single dose of antitoxin. Rosenau and Anderson, in 1906, collected 19 cases from the literature and made the statement that they knew of several more that had not been reported. We all know of instances of sudden death following antitoxin injections which have not been reported in medical literature, but all of these, reported and unreported, were taken together, they probably would not detract from the splendid record of antitoxin more than the minutest fraction of a per cent. These results by no means suggest to us the abandonment of antitoxin, but rather that we should seek some method of separating more completely the antitoxin from the serum, which is the real source of danger.

Von Pirquet and Schiek were the first to consider the aforementioned symptoms, which they found in 20 per cent. of the cases receiving antitoxin, and which they studied together as a distinct disease with its definite incubation period of eight to twelve days; they called it the *serum sickness*.

The frequency of the serum sickness depends on the amount of serum used (Park and Bolduan). When 10 to 30 c.c. of serum was used, 22 per cent. of the cases developed serum sickness. Since using concentrated antitoxin with injections of 5 to 15 c.c. of serum, the number of cases developing symptoms has been reduced to 6.5 per cent. Large injections (100 to 200 c.c.) of Moser's scarlet-fever serum produce serum sickness in 85 per cent. of the cases.

Von Pirquet and Schiek first demonstrated that a second injection of serum produced more rapid and acute symptoms than a single injection. The first dose has a sensitizing effect; the condition produced is the opposite of prophylaxis and is identical with the hypersensitivity produced by Richet in his experiments with congestin and called by him anaphylaxis.

Rosenau and Anderson, in their experimental work on anaphylaxis, have found that in some cases one-millionth of a cubic centimeter intraperitoneally will sensitize a guinea-pig, and that a subsequent dose ten days later of 0.1 c.c. of the same serum will kill the pig. These were exceptionally small doses, but they found the same result quite regularly when larger amounts of a serum were used. Their earlier experiments were made with diphtheria antitoxin, but later, by using normal horse serum, they demonstrated that "the toxic action . . . is caused by a principle in normal horse serum and is entirely independent of the antitoxic properties of the serum."

After establishing that the poisonous principle is inherent in this particular normal serum, they extended their investigations to determine whether it also resided in the normal sera of other animals. For this purpose guinea-pigs were used, and were injected intraperitoneally with the serum of dogs, hogs, cattle, sheep, cats, and rats. Second injections with the same serum have produced either severe

symptoms or caused death, producing in these cases anaphylaxis just as does the horse serum. It has been shown that large doses of normal horse serum, as well as small ones, will produce anaphylaxis in the guinea-pigs. By this work the principle that the serum of one species of animal is poisonous and often fatal to a different species has been well established. A point of interest and much importance lies in the determination of the effect of repeated doses of alien serum on the nutrition of animals to which such serum is not fatal. Repeated injections of horse serum practised by Salter in young guinea-pigs caused retarded growth. Dr. Park's experience with repeated injections into young guinea-pigs of normal horse serum, after killing the complement by heating, is that they 'tend to become cachectic and die.'

Since Harvey's discovery of the circulation of the blood the medical profession at times has had great hopes of finding in the transfer of blood from some healthy source to individuals suffering disease a means of curing many otherwise refractory or incurable maladies. About the middle of the seventeenth century lamb's blood was transfused into the human subject, but it was soon learned that the operation was unsafe, inasmuch as death frequently followed, in consequence of which the practice was discontinued. Many years later direct transfusion was attempted from one individual into the vein of another by means of a cannula. Because of coagulation, thrombosis, etc., the method was abandoned. Attempts have also been made to use intravenously defibrinated blood, but the method is so beset with dangers it is no longer considered safe.

Crile has given us our most recent method of transfusion, and from a surgical standpoint it must be considered an ideal one. A record of the lives that have been saved by this procedure is glowing tribute enough to its merits without entering into any words of praise. However, even here we meet with recitals of sad experiences. It is well known to those familiar with its uses that sudden death sometimes follows the transfer of blood in this way. In these cases air embolism can be excluded as a factor, and we are left with theories to account for the fatalities. Of these, we have red cell embolism, hemolysis, and thrombosis. J. G. Hopkins has demonstrated intravascular phagocytosis of red blood cells. The spreads, made from the blood and bone marrow of a patient who had been transfused and died from the effects, showed polynuclear leukocytes, which had engulfed within their protoplasm from one to five or six red blood cells. This phenomenon suggests the speculation whether, in the transfer of whole blood from one individual to another, the cellular elements are not just so much foreign material which the recipient must destroy and dispose of, and also whether the main virtue in transfusion does not lie in the serum alone.

Under the name of hemophilia neonatorum I report herewith a series of cases, which includes a number of bleeding babies, the etiology

of the hemorrhages in which, as is usually the case, is unknown. In none of the cases was the hemorrhage due to traumatism. Bleeding appears as a rule, during the first week of life, and in this series most frequently on the second, third, and fourth days. The primary bleeding may be from anywhere in the skin or mucous membrane surfaces. However, I have found postmortem that the principal hemorrhage may be either in the brain with extensive laceration, or in the liver (Fig. 1), in which case the capsule may be almost entirely dissected from the surface of the organ; and in addition to these, hemorrhagic spots in other internal organs and effusions



FIG. 1.—Subcapsular hemorrhage of the liver in hemophilia neonatorum.

of blood in the various serous cavities may be found. In some instances I have found the spinal canal filled with fluid blood. The first bleeding may be a slight oozing from the cord at its point of junction with the skin surface and not from the end of the cord due to faulty tying. This cord hemorrhage may persist in spite of all local remedies, and in the course of two or three days a considerable quantity of blood may be lost by this apparently insignificant bleeding. Other bleeding may come from the gastro-intestinal tract, evidence of which is seen in the vomiting of blood or bleeding from the rectum. The lips and gums also frequently bleed. Often the severest hemorrhage appears in the skin, and as a result large hematomas may form which have no relation whatever to traumatism.



Among the list of drugs advocated as therapeutic remedies for this condition the most favorite are probably calcium salts, solutions of gelatin, and adrenalin. Numerous drugs have been employed, but the very length of the list attests their uselessness. In eighteen recorded cases of hemophilia at the Lying-in Hospital, New York, in which these remedies were used there were seventeen deaths, which demonstrates the high mortality in this disease and the futility of all previous therapeutic measures.

Having in mind the almost uniform failure of drugs in this condition and the possibility of producing serum sickness by using the serum of a different species, I decided to attempt the use of normal human serum. In January, 1909, I made my first injections of normal human serum into a bleeding baby.

CASE I.—The subject was three or four days old when it began bleeding. Within twenty-four hours the body was black and blue from subcutaneous hemorrhages; there was a large hematoma occupying one-third of the scalp on one side of the head, and bleeding from the mouth and bowel. The child was so weak it could not cry out when disturbed, though it would make a feeble effort. The case was thought hopeless by the attending surgeon, who requested his house surgeon to ask permission of the parents for a postmortem examination. It was at this time I made the first injection of normal human blood serum; 10 c.c. was used and administered subcutaneously three times during the first day and once each on the following two days. Within a few hours a decided improvement was noted in the condition of the baby, in that the hemorrhages ceased, the old ones began to fade, and strength returned to the child in a very noticeable way. Within three days the hematoma of the scalp was entirely absorbed, and it was quite evident that the child was out of danger. This proved to be true, as the child left the hospital in due time with its mother without any sign of having been a bleeding baby.

Encouraged by this result, the attending physicians of the New York Lying-in Hospital have placed at my disposal for treatment with normal human serum all the bleeding babies that have appeared in their wards. Altogether I have used it in twelve cases, all of which have been cured of their bleeding sickness.

I report herewith eight additional cases, showing the variations in the temperature and weight charts.

CASE II.—First child; female; full term; normal delivery. On the fifth day blood was found oozing from the vulva. During the sixth and seventh days bleeding was continuous. Two hours after applying a fresh napkin the labia and buttocks would be smeared with blood. On the ninth day there was slight oozing from the umbilicus. There was no bleeding after the ninth day. Normal human serum was administered subcutaneously as follows: On the seventh day, three days after bleeding began, 10 c.c. in two doses; on the eighth day,

19 c.c. in two doses; on the ninth day, 22 e.c. in three doses; on the tenth day, 9 c.c. in one dose; total, 60 c.c. in four days (Fig. 2). The total loss of weight was 450 grams, which was reached on the sixth and remained through the seventh day. When the serum was administered the weight began immediately to increase and a steady gain was made later. This baby showed a tendency to sub-normal temperature, which returned to the normal after the bleeding had stopped. It left the hospital in due time in a normal condition.

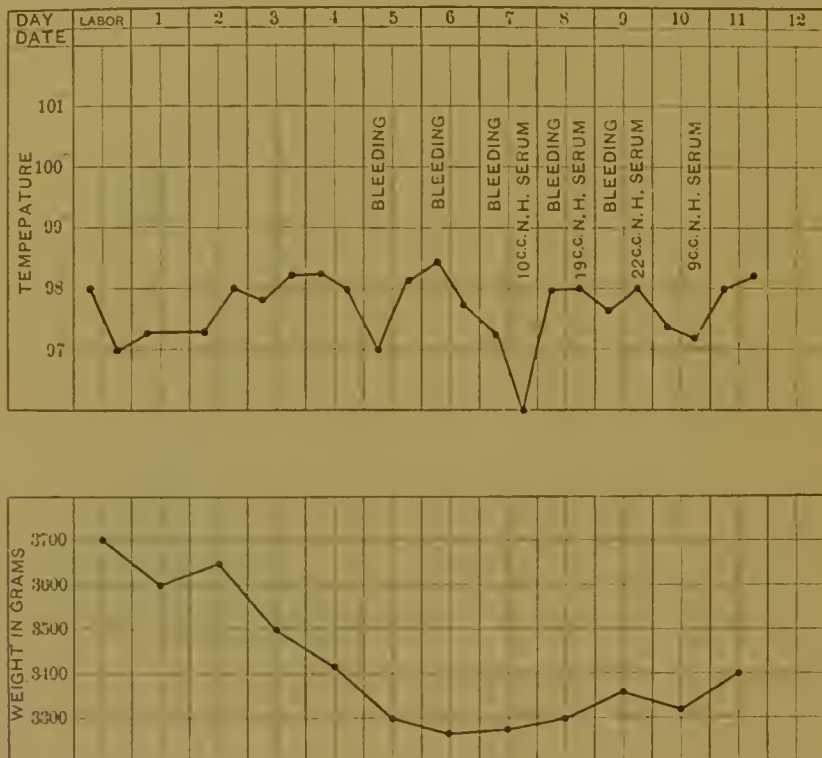


FIG. 2.—Temperature and weight charts of Case II.

CASE III.—Third child; male; full term; high forceps delivery. It showed no bleeding until the seventh day. Then a dorsal division of the prepuce was made for phimosis. During the next four days bleeding recurred about every four hours, often profuse and difficult to control. There was profuse bleeding from the stump of the cord on the seventh day, which continued on the eighth and ninth days, when the stump was invaginated. On the eighth and ninth days there was bleeding from the lips and gums, and on the tenth day subcutaneous hemorrhages appeared on the face. Normal human blood serum was injected subcutaneously as follows: On the eighth day, one day after bleeding began, 10 c.c. in one dose; on the ninth day, 40 c.c. in four doses; on the tenth day, 12 c.c. in two doses;



on the eleventh day, 14 c.c. in two doses; total, 76 c.c. in four days (Fig. 3). The weight of this child ran down steadily until the tenth day, losing altogether 750 grams ( $1\frac{1}{2}$  pounds). Two days after receiving the serum it gained 100 grams, then lost 50, after which it held its own and finally gained. Directly after the bleeding began the temperature rose to  $101.4^{\circ}$ , and it did not go below  $101^{\circ}$  until the bleeding was controlled. This baby was extremely weak and was considered in a serious condition, but was finally discharged from the hospital, with the mother, in good condition.

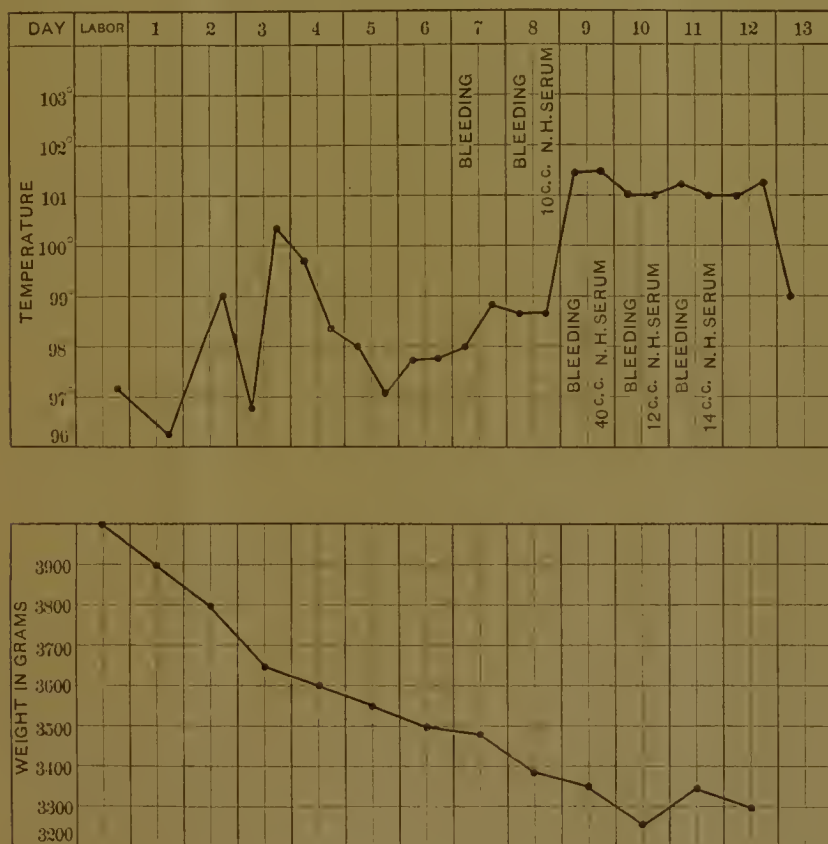


FIG. 3.—Temperature and weight charts of Case III.

CASE IV.—Third child; male; full term delivery by Ccsarean section. On the second day there was slight bleeding from the nose and mouth, and small hemorrhagic spots appeared on the arms and back. The child had embarrassed respiration, attacks of cyanosis and nystagmus. On the third day the hemorrhagic spots increased in size. On the fourth day profuse bleeding from the gums and from the bowels occurred. On the fifth day there was more bleeding from the mouth and rectum and more subcutaneous hemorrhages.

On the sixth day profuse bleeding from the bowels. On the seventh day more subcutaneous hemorrhages in three places on the body. The baby was too weak to nurse, and was fed from a medicine dropper. At this time subcutaneous injections of normal human blood serum were begun and given as follows: On the seventh day, five days after bleeding began, 30 c.c.; on the eighth day, 10 c.c.; on the ninth day, 18 c.c.; on the tenth day, 10 c.c.; on the eleventh day, 10 c.c.; that is, a total, 78 c.c. in five days (Fig. 4). Immediately after administering the serum the temperature, which on the

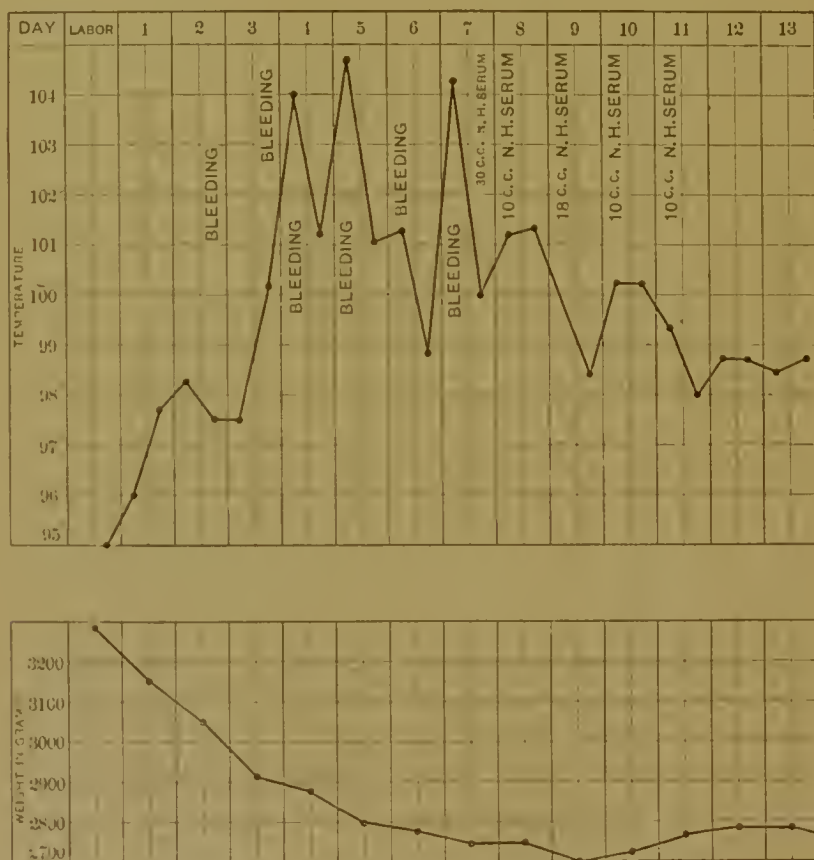


FIG. 4.—Temperature and weight charts of Case IV.

fourth, fifth, and seventh days had been 104° to 104.6°, subsided rapidly to normal, and the weight, which had declined 550 grams, began slowly to rise. This baby had no more bleeding, but was subject to attacks of cyanosis. It had also a rotary nystagmus. On the fifty-sixth day it died, and autopsy showed the cause to be a persistent atelectasis of the lungs involving their posterior half. None of the tissues showed any sign of hemorrhage.

CASE V.—First child; male; full term; normal labor. On the third day blood began oozing from the cord at its junction with the skin, from the foreskin, and there was copious bleeding from the nose. The stools were black, showing altered blood. A single injection of 10 c.c. of normal human serum was given, and within six hours the bleeding ceased and the stools on the following day were normal. There was no more bleeding from this baby (Fig. 5).

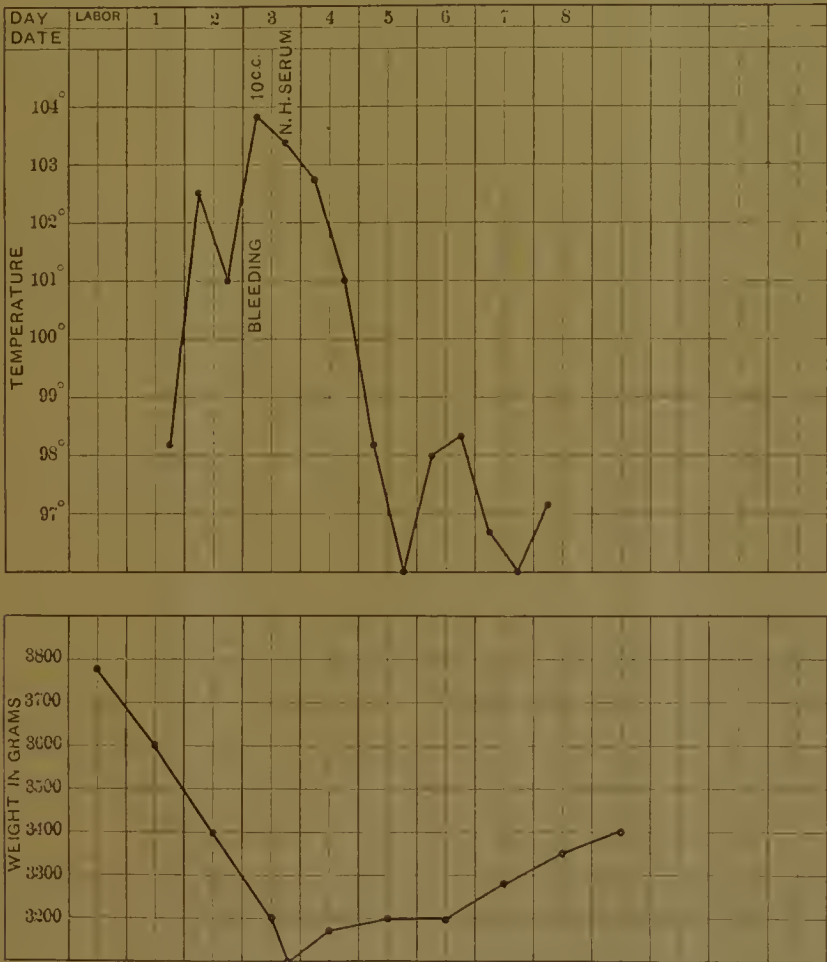


FIG. 5.—Temperature and weight charts of Case V.

CASE VI.—First child; full term; female; normal labor. On the second day it began bleeding from the nose. On the third day it bled from nose and cord, and a large hematoma appeared on the back of the head and neck which extended from ear to ear. There were also subcutaneous bleedings on the right side of the thorax and slight jaundice appeared. On the fourth day there was bleeding from the nose and gums and blood was passed in the stools. The hemor-

rhage in the neck increased, and fresh ones appeared on the scalp and right wrist. On the fifth day slight bleeding from the nose; one spot was noticed on the right knee and left elbow. Normal human serum was injected as follows: On the fourth day, two days after bleeding began, 35 c.c. in three doses; on the fifth day, 20 c.c. in two doses; on the sixth day, 29 c.c. in two doses; on the seventh day, 27 c.c.; on the eighth day, 12 c.c.; total, 123 c.c. in five days (Fig. 6). There was no more bleeding after the fifth day, and the child was discharged on the thirteenth day normal.

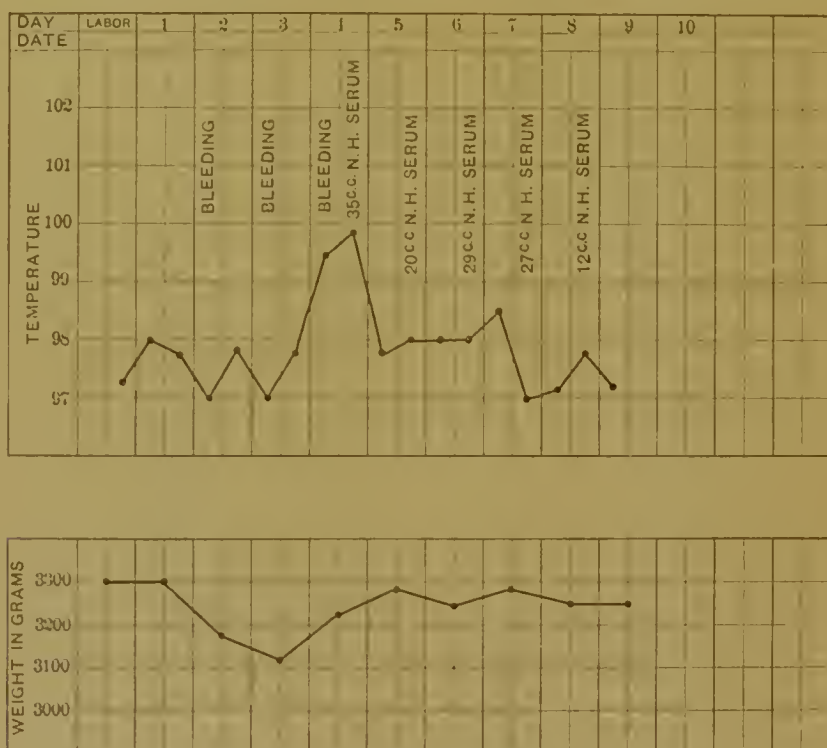


FIG. 6.—Temperature and weight charts of Case VI.

**CASE VII.**—First child; female; full term; normal labor. Bleeding from the cord and rectum began on the fourth day. On the fifth day bleeding from the vagina and rectum, and two subcutaneous hemorrhages appeared on the left side of the thorax. On the sixth day profuse bleeding from the cord and slight bleeding from the rectum. There was no bleeding on the seventh and eighth days, and no serum was administered in consequence. On the ninth day there was vomiting of blood and slight bleeding from the rectum. On the tenth day profuse bleeding from the cord, vomiting of blood, and bleeding from the rectum, two subcutaneous hemorrhages on the right side of the thorax, and others on the elbows and on the back. No further bleeding after the tenth day. Normal human blood serum was administered subcutaneously as follows: On the fifth day,

one day after bleeding began, 10 c.c. in one dose; on the sixth day, 20 c.c. in two doses; on the ninth day, 20 c.c. in two doses; on the tenth day, 10 c.c. in one dose; on the eleventh day, 8 c.c. in one dose; on the twelfth day, 5 c.c. in one dose; on the thirteenth day, 10 c.c. in one dose; total, 83 c.c. in seven days (Fig. 7). The bleeding in each attack was controlled on the second day. This chart illus-

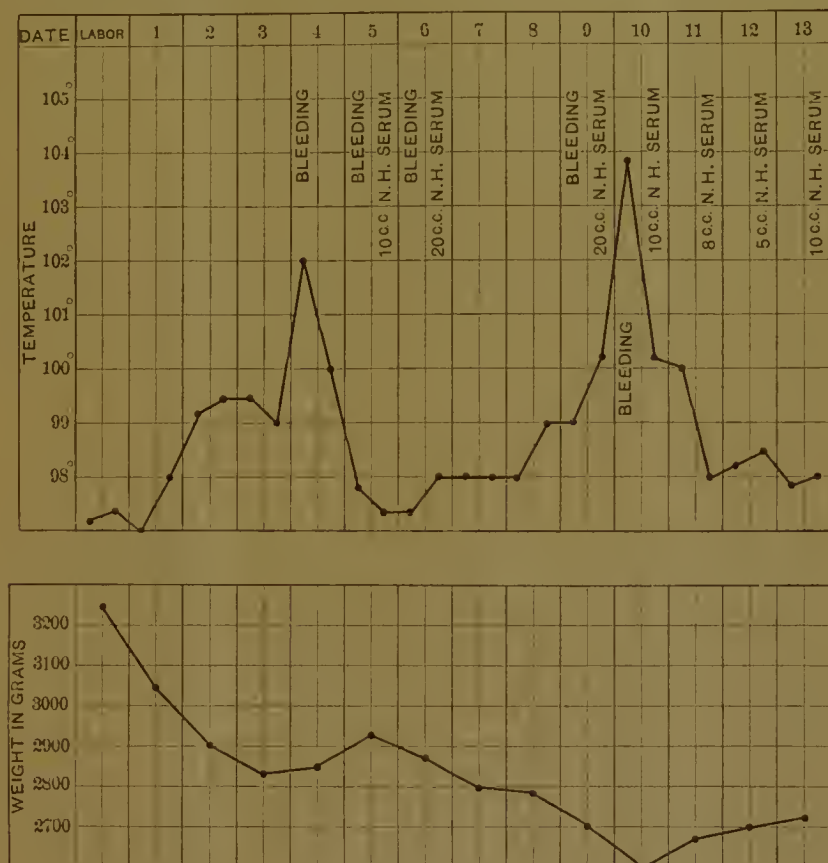


FIG. 7.—Temperature and weight charts of Case VII.

trates twice the manner in which the temperature and weight curves diverge during the bleeding, and how they approach each other when bleeding stops.

CASE VIII.—First child; male; full term; normal labor. On the third day began bleeding from the mouth and rectum. On the fourth day profuse bleeding from the mouth, nose, rectum, and under the skin covering the left scapula. On the fifth day bleeding continued. No bleeding on the sixth day. On the seventh day bleeding from the rectum. No bleeding after the seventh day. Normal human blood serum was injected subcutaneously as follows: On the sixth day, three days after bleeding began, 7 c.c. in one dose; on the seventh day, 9 c.c. in one dose; total, 16 c.c. in two days (Fig. 8).



CASE IX.—First child; full term; male. Mother had a post-partum hemorrhage. At 4 A.M. on the fourth day it had a large hemorrhage from the bowel and vomited blood-stained fluid. At

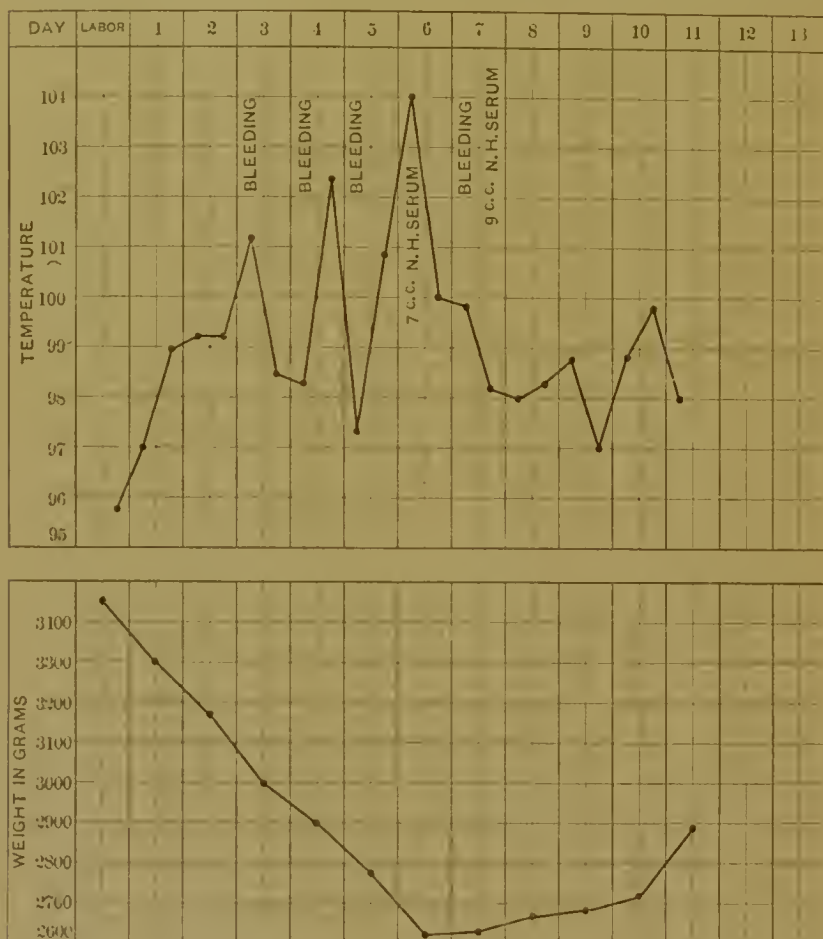


FIG. 8.—Temperature and weight charts of Case VIII.

4.30 A.M. had very profuse hemorrhage from the bowel and vomited small amount of blood. At 10.30 A.M. bleeding from the rectum and vomiting of a small amount of blood. At 11 A.M. hemorrhage from the rectum, and small amount of blood vomited. Baby was very weak, not able to cry out when injected. Pale and jaundiced, waxy looking. The house physician said baby had lost half its blood. At 2.15 P.M. small hemorrhage from the rectum; 3.00 P.M., severe hemorrhage from the rectum; 7 P.M., small amount of slightly blood-stained vomitus, small blood clots in the feces; 10.30 P.M., blood clots in the stools, slight hemorrhage from the nose, mouth, and rectum. March 23, the fifth day, 8 A.M., vomited small amount of blood; 10 A.M., large amount of blood from the rectum, which was the last bleeding. Normal human blood serum was injected subcutaneously as follows:

On the fourth day, day hemorrhage began, 64 c.c. in six doses; on the fifth day, 65 c.c. in six doses; on the sixth day, 30 c.c. in three doses; on the seventh day, 22 c.c. in two doses; on the eighth day, 28 c.c. in three doses; total, 209 c.c. in five days (Fig. 9).

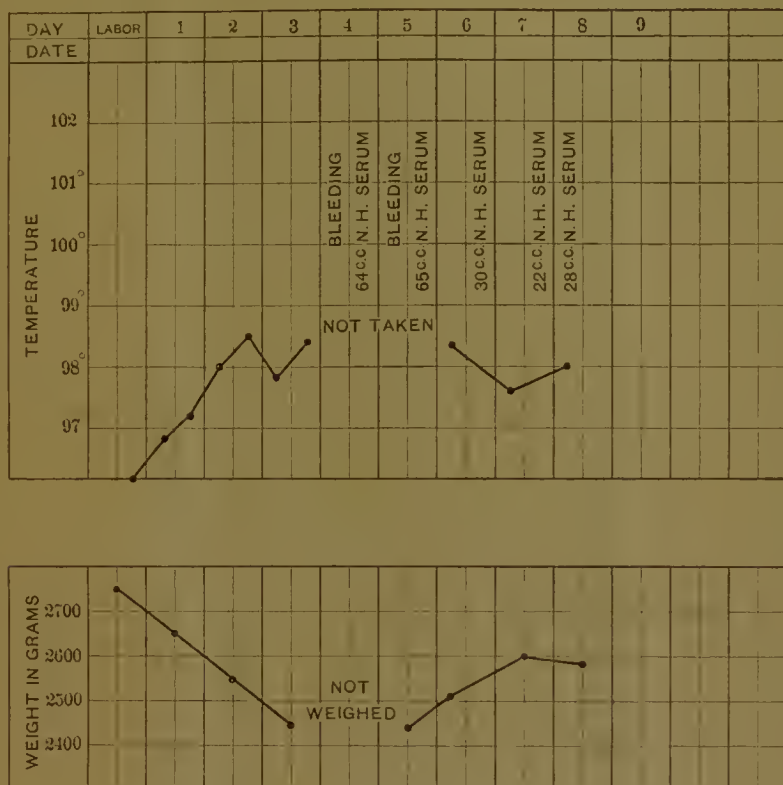


FIG. 9.—Temperature and weight charts of Case IX.

In normal human serum we find an agent that successfully controls hemorrhage in the newborn. I have not gone into the theories as to the causes of these hemorrhages. They are probably due to different factors. In none of the cases could a history of bleeding in the antecedents be obtained. It is possible that some were true cases of hemophilia, while others were due to some infection. In my postmortem experience I have found, as have others, that the hemorrhages are sometimes due to a bacteremia caused by the streptococcus, staphylococcus, and in some cases a bacillus. I have reason to believe that, even though the bleeding be due to bacteremia, the normal human serum will still be an effective therapeutic agent.

It has been demonstrated so frequently that it is now a matter of common knowledge that fresh normal human blood serum is often bactericidal. If put into the body of a baby in sufficient quantity, and kept moving by the circulation to elimination, it must surely exert this bactericidal effect. I have used it in repeated small and

large doses, also in single small and large doses, and am ready to state positively that it never gives serum sickness or causes anaphylaxis in the human subject. On the other hand, it is a perfect form of food, already digested and ready to be taken up and utilized by the tissues and cells of the body, so that without dissipation of energy regeneration may progress with a maximum of efficiency. In many of these babies with bleeding from the gastro-intestinal tract, nourishment from this source is impossible. The alimentary tube is filled with decaying blood, and in most instances there is reversed peristalsis, which militates against digestion, and, added to these, there exists a clouding of the epithelium and considerable desquamation. The food cannot be properly prepared for absorption, and should it be, the circulation is so feeble as to be an obstacle to its removal into the tissues.

When placed under the skin normal human blood serum is quite readily removed from the site of injection. I have seen two ounces completely removed within five minutes by gently massaging the skin over the site of injection while administering the dose. As a further testimonial to the harmless effect of human blood serum, I will refer to some of my work in connection with eclampsia, in which I injected 150 c.c. of serum, removed from an eclamptic patient by venesection, after her twentieth convulsion, into a normal adult, within twenty-four hours, without the slightest noticeable effect, either subjectively or objectively. This patient died of her eclampsia shortly after the venesection.

It may be that the hemorrhage is partly and in some cases entirely controlled by the nutritive effect on the body tissues of the infant. In others it is possible that a thrombokinase is supplied, as suggested by Kottman and Lidsky, who obtained it from animal sera and from the filtrate of the chopped and soaked rabbit livers which they applied locally to check hemorrhages about the cord.

As to the dose of serum to be used in any given case, it should be said that this depends upon the urgency of the case. One is apt to err on the side of too small doses. It is advisable to begin with at least 10 c.c., and repeat three times per day if the infant is bleeding only moderately. In severe cases it should be given every two hours, and in larger quantities if necessary. It is very important to begin the treatment at the first indication of bleeding, however apparently insignificant. Slight bleeding of the cord may be accompanied by fatal internal hemorrhage if not stopped immediately.

The blood is very easily collected. The apparatus (Fig. 10) I have devised consists of a rubber cork through which are two perforations. Through one perforation is fitted a U-shaped glass tube, to the outer end of which is attached, by means of a piece of rubber tubing, a short aspirating needle having a No. 19 caliber. The needle is cotton-plugged into a small test-tube, in which it is sterilized. Through the other perforation is inserted a fusiform glass tube containing cotton to prevent contaminating the contents of the flask.

A small suction tube is placed on this latter for drawing the blood into the flask. The needle is inserted into a vein at the elbow and the desired amount of blood withdrawn. The blood is allowed to coagulate in a slanting position in the flask, and the serum is withdrawn as rapidly as it separates, and it is then ready for use.



FIG. 10.—Apparatus for collecting the blood serum.

I have also used subcutaneous injections of normal human blood serum in a case of streptococcemia, with an apparent good effect. The patient's temperature was normal until the third day post-partum, when it rose to  $104^{\circ}$  F. On the fourth day an intra-uterine culture developed a growth of streptococci and staphylococci. A blood culture on the sixth day proved sterile. The patient's temperature remained high, so that notwithstanding a negative blood culture she was considered to be suffering with bacteremia. In consequence she was given Hiss' extract of leukocytes on the seventh, ninth, tenth, and eleventh days. The temperature seemed to react well for a few days under this treatment, but finally rose again on the twelfth day to  $104.8^{\circ}$  F., and the patient's condition was very bad. A second blood culture, made on

the tenth day postpartum, developed a pure growth of streptococci. The patient was considered in a hopeless condition from the twelfth to the fifteenth day. On the fifteenth day she received 20 c.c. of normal human blood serum hypodermically, and on the sixteenth, seventeenth, and eighteenth days each 10 c.c. She had no rise of temperature after the nineteenth day. A blood culture made on the twenty-seventh day developed no growth of organisms. The patient was dismissed from the hospital in a normal condition. Fig. 11 illustrates the temperature curve and the pulse rate in this case.

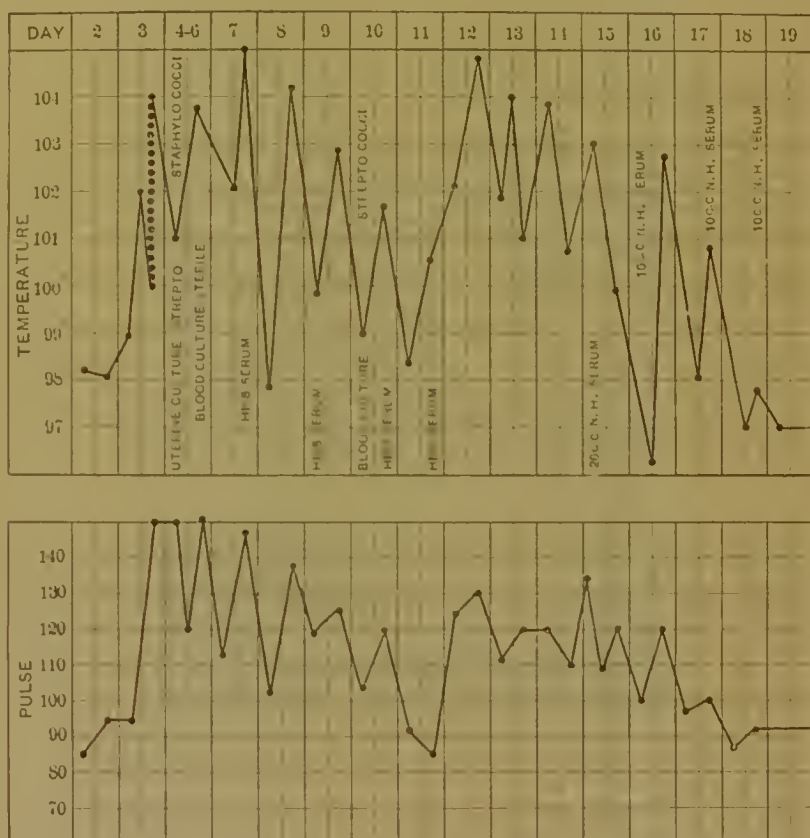


FIG. 11.—The temperature curve and the pulse rate in a case of streptococcemia.

Normal human blood serum administered hypodermically to tuberculous individuals gives excellent results. According to Wright, normal human blood serum contains more opsonin than that of a tuberculous person, and it may be through this property, causing more complete phagocytosis, that the benefit in this condition is derived.

Normal human blood serum has a broader field of application than in the cases herewith mentioned. By means of work now in progress I hope to demonstrate its value in other conditions.





the simula  
Williams, T  
oyal Coll  
ov 11, 20

